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EXAMINER	
ROARK, JESSICA H	
ART UNIT	**PAPER NUMBER**
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/524,531	Applicant(s) IMHOF ET AL.	
	Examiner Jessica H. Roark	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,10,12,13,20 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,10,12,13,20 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 November 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

RESPONSE TO APPLICANT"S ARGUMENTS

1. Applicant's amendment, filed 4/1/03 (Paper No. 29), is acknowledged.
Claims 3-9, 11 and 14-19 have been canceled.
Claims 20 and 21 have been added.
Claims 1, 2, 10 and 12 have been amended.
Claims 1-2, 10, 12-13 and 20-21 *are pending and under consideration.*

Sequence Compliance

2. Sequence compliance: Applicant's provision of a corrected CRF, Sequence Listing, and Statement that the contents are identical on 7/29/02 (Paper No. 23), is acknowledged. The CRF has been found acceptable and entered. However, Applicant is required to identify the nucleotide and amino acid sequences with SEQ. ID NOS wherever sequences occur in the specification, drawings, and claims, in order to full satisfy the requirements of 37 CFR 1.821 (d) (see also MPEP 2422.02-2422.03).

It is noted that Figures 2, 4, 5 and 8 have sequences for which no sequence identifiers appear either in the Figures or in the Brief Description of the Drawings, and that the Description of Figure 7 includes neither all the amino acid sequences in the Figure nor the nucleotide sequences of Figure 7.

Applicant is again requested to carefully review the specification. Appropriate correction is required.

Drawings

3. The drawings submitted 11/15/02 have been approved by the Draftsman.

4. Applicant is reminded to amend the Brief Description of the Drawings to provide sequence identifiers for any sequence present in Figures but lacking an identifier in the Figure.

Appropriate correction is required.

Priority

5. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Priority document EP 99200746.8 (filed 3/11/1999) does appear to provide adequate written description of the murine CRAM-1 polypeptide of SEQ ID NO:13 and a soluble form thereof that can inhibit transendothelial migration of leukocytes. The priority document also appears to provide an adequate written description of the domain structure of SEQ ID NO:13 which includes an extracellular V and extracellular C2 domain as set forth in Figure 2 of the priority document.

However, priority document EP 99200746.8 does not appear to provide adequate written support for a human CRAM-1 polypeptide, including the polypeptide of SEQ ID NO:15, or for any forms thereof. Neither does priority document EP 99200746.8 appear to provide adequate written support for a membrane proximal cytoplasmic sequence defined by amino acids 266-272 of SEQ ID NO:13. In addition, language supporting a genus of CRAM-1 polypeptides having "essentially 100% sequence homology" does not appear to be present in the priority document.

6. This Office Action will be in response to applicant's arguments, filed 4/1/03 (Paper No. 29). The rejections of record can be found in the previous Office Action (Paper No. 18).

It is noted that New Grounds of Rejection are set forth herein.

Claim Rejections - 35 USC § 112 second paragraph

7. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1, 2, 13, 20 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1, 2, 13, 20 and 21 are indefinite in reciting "modulating" because it is ambiguous as to the direction (positive or negative) or degree of said modulating. It is suggested that Applicant amend the claims to indicate whether the "modulating" is inhibitory or stimulatory.

B) Claims 1, 2 and 13 are indefinite in the recitation of vascular endothelium "function" because the metes and bounds of the vascular endothelial functions encompassed are unclear. It is suggested that Applicant amend the claims to recite a particular function of the vascular endothelium. Alternatively, it is noted that for claim language limited to defined sequences (e.g., an isolated polypeptide as set forth in SEQ ID NO:15), a recitation of function is not required.

C) The phrase "having essentially" in claim 21 is a relative term which renders the claim indefinite.

Applicant argues in the Remarks filed 4/1/03 that a polypeptide having essentially 100% sequence homology is a polypeptide having only minor variation and possessing the same function as the referenced SEQ ID NO:.

However, the Examiner maintains that the ordinary artisan would not be able to recognize the metes and bound of the limitation in the context of the instant claim. While the Examiner acknowledges that in many claim constructions "having essentially" would simply open the claim up to inclusion of subject matter that would not materially affect the basic and novel characteristics of the material claimed; in the instant case the language is presented in the context of variation within a core structure. The specification does not describe what are the metes and bounds of changes that can be made such that a polypeptide has essentially 100% sequence homology. An argument that any variant polypeptide that maintains the recited function "has essentially 100% sequence homology" means there is no clear upper limit on the number of amino acid changes that can be made and still result in a polypeptide that "has essentially" 100% sequence homology.

Therefore, Applicant's arguments with respect to the instant claim construction encompassing variation in the core polypeptide sequence are not found convincing. The Examiner maintains that one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention as currently claimed.

D) Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

Claim Rejections - 35 USC § 112 first paragraph

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-2, 10, 12-13 and 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the amino acid sequences of SEQ ID NO:13 and SEQ ID NO:15 and certain soluble polypeptides which inhibit transendothelial cell migration of leukocytes; does not reasonably provide enablement for the genus of "vascular endothelial functions" which may be modulated, or for a "part" of the amino acid sequence, other than a part that is the extracellular domain, having any particular functions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant's arguments, filed 4/1/03, have been fully considered but have not been found convincing.

Applicant asserts that the claims as amended are fully enabled at least because the specification indicates (e.g., on pages 6-7) that soluble polypeptides having essentially the same amino acids sequences as CRAM polypeptides are functional and capable of targeting the vascular endothelium. Applicant concludes that any amino acid sequences mutations or deletions must therefore be at positions that do not eliminate the functional capabilities recited in the instant claims.

Applicant has disclosed two amino acid sequence (SEQ ID NO:13 and SEQ ID NO:15) with a disclosed function of vascular adhesion and leukocyte transmigration (e.g., pages 25-28). The specification also identifies an extracellular region comprising the V and C2 domains, a transmembrane domain, and a cytoplasmic domain (e.g., Figure 8 and Brief Description of Figure 8 on page 9). A fusion protein comprising the fragment of the polypeptide ending with the sequence DGV (amino acids 289-291 of either SEQ ID NO:13 or SEQ ID NO:15) is also disclosed (e.g. page 17 of the specification in view of SEQ ID NO:13 and SEQ ID NO:15), as are fusion proteins comprising either the single Ig (V) domain or the two domains of the extracellular region (VC2) (e.g., bridging paragraph of pages 17-18).

First it is noted that not all claims recite a function for which the metes and bounds are clear, as noted supra. Thus although the specification does appear to provide sufficient guidance with respect to the functions of inhibiting or supporting transendothelial cell migration of leukocytes or vascular permeability; there does not appear to guidance commensurate in scope with functions that involve "modulation of the vascular endothelium" in general.

The Examiner again acknowledges that sufficient guidance has been provided as to how to make and use certain "parts" of the amino acid sequences, such as a fusion protein comprising the extracellular region which was disclosed to inhibit leukocyte transmigration (e.g. page 27 at lines 26-31). However, the instant claims require certain functions for which the specification does not appear to provide sufficient guidance as to which "parts" of the polypeptides are essential to that function. Thus although sufficient guidance has been provided that a soluble polypeptide comprising the extracellular domain would possess the function of inhibiting migration of leukocytes, the Examiner maintains that a person of skill in the art would not be able to determine without undue experimentation which of the plethora of other polypeptide "parts" of the amino acid sequence would share this ability, or would have the other recited "functions".

As previously noted, Aurrand-Lions et al. (Blood 2001; 98:3699-3707, of record) teach that although the instant mouse and human polypeptides (which they call JAM-2) have homology to other molecules also shown to be involved in vascular adhesion (i.e., JAM-1 and JAM-3), the differences in the amino acid sequences between these molecules result in differences in expression and function with respect to their regulation of vascular permeability (see entire document, e.g., Abstract). Thus even though a comparison of JAMs indicates a similar overall structure as identified by the V, C2, transmembrane and cytoplasmic domains; the structural similarity and homology of the JAMs still does not permit the skilled artisan to identify which sequence fragments are essential for a particular function since the individual homologous JAMs have distinct functions.

In the absence of additional guidance as to which "parts" of the instant polypeptides provide a particular function and as to what that particular vascular endothelium function actually is, a person of skill in the art would not know which other sequences are essential, which sequences are non-essential, and what particular sequence lengths identify essential sequences for a given function. Thus for other than those fragments identified clearly in the specification by both sequence length *and* associated function; there is insufficient guidance to direct a person of skill in the art to select other undisclosed sequences or sequence lengths as essential for a particular function, and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

11. Applicant's amendment has obviated the previous rejection of claims 1-2, 10 and 12-13 under 35 U.S.C. 112, first paragraph, written description , by limiting the instant claims to either discrete sequences, or sequences with limited amino acid sequence variation coupled with a function.

Claim Rejections – 35 U.S.C. § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 2, 10, 13 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Dumas Milne Edwards et al. (WO 99/06551, of record).

Applicant's arguments, filed 4/1/03, have been fully considered with respect to the pending claims, but have not been found convincing.

As previously noted, Dumas Milne Edwards et al. teach the polypeptide of SEQ ID NO:294 and methods for expressing and isolating this polypeptide (see pages 1-13, 114 and 253).

The polypeptide of Dumas Milne Edwards et al. comprises an amino acid sequence that is 100% identical to SEQ ID NO:15 over residues 1-89. The polypeptide of Dumas Milne Edwards et al. would inherently be soluble since it does not encompass a transmembrane domain.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the polypeptide of SEQ ID NO:294 taught by Dumas Milne Edwards et al.

Applicant argues that the polypeptide of SEQ ID NO:294 is an EST for which no function is assigned, and asserts that the polypeptide would not inherently possess the instantly recited functions.

The Examiner acknowledges that no function is assigned to the polypeptide by Dumas Milne Edwards et al. However, the function of a polypeptide is inherent in its sequence. It is noted that the instant claims do not require the full length polypeptide of SEQ ID NO:15, but rather are drawn to any "part" of the polypeptide having the recited functions.

Applicant has provided no evidence that the polypeptide of Dumas Milne Edwards et al. would not modulate vascular endothelium permeability and inhibit transendothelial migration of leukocytes. The Examiner is not in a position to test whether or not the "part" of SEQ ID NO:15 taught by Dumas Milne Edwards et al. has the recited function. Rather, the burden is on the applicant to establish a patentable distinction between the claimed "part" of the amino acid of SEQ ID NO:15 and the polypeptide taught by Dumas Milne Edwards et al.. See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and In re Fitzgerald et al., 205 USPQ 594 (CCPA 1980).

The rejection of record is therefore maintained as applied to the instant claims.

Conclusion

14. No claim is allowed.

15. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 305-3014.

Jessica Roark, Ph.D.
Patent Examiner
Technology Center 1600
July 16, 2003

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